Gene–Environment Interaction in Neurodegenerative Disease

There is provocative evidence that environmental exposures to certain neurotoxicants (heavy metals, pesticides, fungicides) may play a role in the development of neurodegenerative movement disorders such as Parkinson disease (PD) and amyotrophic lateral sclerosis (ALS). Recent research on these diseases has focused on both the underlying biological processes critical to disease manifestation for the development of new treatments and the relative roles of neurochemical and genetic factors in their etiologies. Much work, however, remains to be done to clarify these fundamental processes.

The objective of this three-year program announcement (PA) is to stimulate research on the relative roles of neurochemical and genetic factors in the causation of neurodegenerative diseases. This new initiative will selectively shift its research focus each year to emphasize a different neurodegenerative disease. In the current year, the special focus is on soliciting research on gene–environment interactions as a risk factor in ALS (a fatal disease of unknown etiology marked by the progressive degeneration of motor neurons) in order to stimulate much-needed research in this area. In succeeding years, there will be an announcement indicating a different neurodegenerative disease focus area.

Several epidemiological studies have implicated gene–environment interactions in the development of PD and ALS. Nevertheless, it is still not clear whether differences in prevalence rates or clusters of these diseases in various communities are due to the differential distribution of a hypothetical environmental toxicant or are more frequent where a familial heritable defect is more common. To date, analytic epidemiological studies have varied in case and control selection methodology and venues (e.g., clinics, population bases, different countries), partly accounting for the disparate conclusions reached by some investigators. While a good deal of research has been devoted to the influence of the environment in the susceptibility to PD, there has not been a similar effort committed to ALS.

Some progress has been made in recent years toward understanding the biological bases of ALS. A number of pathological, biochemical, and electrophysiological abnormalities are found in affected patients and are seen in postmortem nervous tissues. Markers for genes in familial ALS (FALS), both dominant and recessive, have been identified, but they represent only a portion of the possible gene loci. In 15–20% of FALS cases, there is a mutation of the copper/zinc superoxide dismutase (*SOD1*) gene on chromosome 21. However, the overwhelming majority of ALS patients do not have this mutation. Genetic studies of ALS linked to other chromosomes are needed, especially of those genes easily influenced by neurotoxicants.

It is significant that the first descriptions of ALS coincided with the Industrial Revolution. Therefore, it has been logical to consider whether environmental contamination associated with increased levels of industrial activity might be implicated in its pathogenesis. The possible role of occupational exposures in ALS has also been investigated. Epidemiological studies have implicated heavy metals and other environmental exposures as risk factors for ALS but as yet have not provided a clear directional lead. For example, various studies have looked at occupational exposure to lead, mercury, selenium, manganese, aluminum, and iron exposure in assessing risk factors for the disease. Calcium has also been studied because of suggestions that excitotoxicity and calcium channel antibodies may be implicated in its etiology. In addition, in some areas, agricultural workers seem to have a higher risk of developing ALS, whereas studies on exposure to industrial solvents and chemicals have brought mixed results.

No coherent picture has emerged from these studies, however, nor have many of them been correlated with genetic studies. Therefore, much remains to be learned about the mechanisms through which genetic mutations and other biological insults lead to pathology. The genetic defects identified in FALS have lead to the development of some useful animal models of the disease, but more models are needed to expand research on the abnormal biology of the affected motor neuron and nonneuronal cells, on nervous system response to endogenous and environmental toxins and toxicants, and on identification of metabolic, endocrine, and immunological abnormalities.

Additional research is also needed to understand the contribution of environmental exposure, endogenous susceptibility factors, and increasing age in the disease linkage. This will require a concurrent advancement and refinement of methodologies and sciences. Of particular significance may be those approaches that can be used across species from lower animals to humans. Such approaches permit a precise characterization in animal models of alterations arising from defined environmental exposures that can serve as a cogent guide to underlying cellular and molecular mechanisms in humans.

This initiative will seek to solicit novel approaches to understanding ALS, with emphasis on the role that gene–environment interactions may play in the above. Examples of research goals that could be pursued, especially in appropriate animal models and tissue culture, include (but are not limited to) the following:

1) development of animal models of ALS, especially nonmammalian models useful for gene–environment research;

2) development of biomarkers of exposure and disease in animal models (using metabonomics, for example);

3) research on modifier genes and environmental influences in animal models;

4) studies on the intersections and synergies between genetic susceptibilities and environmental factors, as well as strategies for identifying putative toxicants and other environmental factors involved in the etiology of ALS;

5) establishment of disease incidence and variation according to age, gender, race/ethnicity, geography, and exposure;

6) studies on potentially informative clusters (Western Pacific ALS/parkinsonism–dementia complex [PDC], Persian Gulf War veterans, Kelly Air Force Base workers, etc.);

7) studies on occupational/environmental exposures and nonoccupational exposures (evidence for the role of metals, pesticides, solvents, residential/avocational exposures, tobacco, alcohol, infectious agents);

8) research on the potential role of dietary excitotoxins in Western Pacific ALS/PDC and analogies with other disorders;

9) research on the role of dietary intake of antioxidants and minerals (copper, zinc, iron), and the association of fat and fiber intake with ALS;

10) research on factors targeting putative environmental toxicants specific to motor neurons and surrounding cells including muscle cells;

11) research on disease mechanisms on the cellular or subcellular level (oxidative stress, excitotoxicity, apoptosis) from neurotoxic exposures; and

12) evaluation of retrograde axonal transport of toxins to the spinal motor neurons and their response (access and possible uptake of toxic substances at the neuromuscular junction).

Moreover, the NIEHS would like to encourage multidisciplinary and interdisciplinary studies. What may be especially useful are collaborations with ongoing research in other motor disorder diseases that could be expanded to include ALS studies. We also encourage the use of novel animal models such as *Drosophila*, zebra fish and *C. elegans*, as well as newly available technologies. Especially useful would be collaborative pooling of resources to standardize epidemiological instruments, microarray analyses, "-omics" technologies, and other methods and materials for meaningful use among several laboratories.

This PA will primarily use the NIH Research Project Grant (R01) and Exploratory/Developmental Grant (R21) award mechanisms (though, if appropriate, competitive supplements may be considered if it is to accomplish collaborations). This PA uses just-in-time concepts. It also uses the modular as well as the nonmodular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise, follow the instructions for nonmodular research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

The NIEHS intends to commit approximately $2 million in fiscal year 2004 to fund 10–15 new grants in response to this PA. An applicant may request a project period of up to five years for R01 grants and up to two years for R21 grants. Direct costs for R21 grants may not exceed $275,000. The characteristics, requirements, preparation, and review criteria for R21 applications are described at http://grants.nih.gov/grants/guide/pa-files/PA-03-107.html.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format.

Applications submitted in response to this PA will be accepted at the standard application deadlines, which are available at http://grants.

nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit. Complete information on this PA is located at http://grants1.nih.gov/grants/guide/pa-files/PAS-03-160.html.

Contact: Annette Kirshner, Cellular, Organs, and Systems Pathobiology Branch, Division of Extramural Research and Training, NIEHS, PO Box 12233, MD-23, Research Triangle Park, NC 27709 USA, 919-541-0488, fax: 919-541-5064, e-mail: kirshner@niehs.nih.gov. Reference: PA No. PAS-03-160

International Bioethics Education and Career Development Award

The Fogarty International Center (FIC), in partnership with the National Center for Complementary and Alternative Medicine (NCCAM), the National Heart, Lung, and Blood Institute (NHLBI), the National Human Genome Research Institute (NHGRI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Drug Abuse (NIDA), the National Institute of General Medical Sciences (NIGMS), and the NIEHS, invites applications to develop or expand current graduate-level curricula and training opportunities in international bioethics related to performing research involving human subjects in low- and middle-income nations. As current programs provide training for participants from the Asian, African, and Latin American regions (for descriptions of current programs, see http://www.fic.nih.gov/programs/bioethics/bioethicsaward.html), new applications focusing on countries of the Middle East; North, East, and West Africa; Eastern Europe; and the former Soviet Union are encouraged.

Applicant institutions can request up to four years of support to create comprehensive curriculum development and training programs. Developing country institutions can request up to two years of support for program planning and curriculum development in preparation to apply for comprehensive training program support in the future. In addition, current International Bioethics Education and Career Development awardees may apply for competing supplements to their award to collaborate with other FIC programs (for descriptions of other programs, see the FIC web site: http://www.fic.nih.gov/programs.html).

Proposed curricula should provide a core set of advanced study courses that focus primarily on the internationally relevant aspects of the ethical, legal, and social principles guiding the responsible conduct of research in developing countries. Support will be provided for training developing-country health professionals working at institutions conducting biomedical, behavioral, or public health research involving human subjects, and for ethicists or philosophers from developing countries with an interest in biomedical/clinical research. Appropriate training may include advanced degree– and nondegree-associated course work and practicum experiences such as participation in ethical review committees, development of intensive short courses designed for members of human subjects research ethical review committees, analysis of ethical review guidelines or processes, and research on ethical practices in biomedical or behavioral research in the trainees' countries.

This request for applications (RFA) contributes to the FIC's initiative to strengthen research bioethics expertise in developing countries. This RFA is intended to stimulate the development of new instructional programs in international bioethics at institutions that do not currently offer such programs, and to expand existing instructional programs in international bioethics to include a major focus on issues relevant to developing countries. The goal of this initiative is to increase the cadre of biomedical and behavioral scientists, clinical investigators, nurses, and other health professionals and relevant academics in developing countries with state-of-the-art knowledge of ethical considerations, concepts, and methods in research involving human subjects. It is expected that such advanced training will enhance the career development of individuals from developing countries as well as strengthen bioethical expertise at the trainees' host institutions.

Few developing-country institutions provide formal training in bioethics, and few developed-country programs for advanced bioethics training focus in depth on the internationally relevant aspects of bioethics, particularly those related to clinical investigations and traditional medical interventions in developing countries. Therefore, few developing-country health professionals conducting laboratory or clinical investigations have received extensive training in the principles of bioethics, codes, and legal aspects of ethical research, ethical experimentation on vertebrate animals, informed consent, decision making related to collaborative agreements between hosts and sponsors of clinical research, elements of study design that affect the ethical conduct of clinical trials, or interventions that should be provided to study participants.

This initiative seeks to train academics, health professionals, and researchers from developing countries in culturally relevant bioethics related to research. Proposed training programs should equip them with the critical skills that are needed to provide bioethics expertise and leadership to their institutions, national governments, and international bodies, and potentially, to pursue studies on ethical practice in biomedical and behavioral research in developing countries. The specific objectives are as follows.

1) ***Curriculum development to improve the quality of international ethics training.*** This will be achieved by supporting the development of courses in fundamental areas needed to provide skills for teaching and research related to bioethics and the ethical review of research on acute and chronic diseases in developing countries. Curriculum should include topics most relevant to the bioethics issues widely experienced in conducting research involving human subjects in resource-poor settings in developing countries. These include voluntary informed consent, standards of medical care, sensitivity to cultural differences, research on vulnerable populations, benefits sharing, use of human biological materials, human rights, conflict of interest, equivalent protections, and harmonization of international guidelines. Applicants are encouraged to develop training modules including topics related to the specific research interests of the participating NIH institutes and centers listed above.

2) ***Training to support appropriate advanced training for a cadre of developing-country professionals who could assume the expert roles and leadership responsibilities when involved in ethics review, clinical trials, and epidemiological studies in their countries.*** Applications that provide training for participants from the Middle East; North, East, and West Africa; Eastern Europe; and the former Soviet Union are particularly encouraged.

This RFA will use the NIH R25 award mechanism that limits facilities and administrative (F&A) costs to 8% of direct costs (less equipment). Applicants that request funding for subcontracts to foreign organizations may also include F&A costs up to 8% of direct costs (less equipment). More information on the F&A costs allowed for foreign institutions and international organizations can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-028.html. The anticipated award date is June 2004.

The participating institutes and centers intend to commit approximately $1.8 million in fiscal year 2004 to fund 7–8 new and/or competitive continuation awards and planning/curriculum development grants in response to this RFA.

For comprehensive curriculum development and training program awards, an applicant may request a project period of up to four years and a budget for total costs of up to $250,000 per year maximum (including 8% F&A costs).

For planning and curriculum development grants, developing-country applicants can request up to two years of support for a program for up to $25,000 total costs per year (including 8% F&A costs).

For competing supplements, principal investigators of active International Bioethics Education and Career Development awards may request a supplement of up to $25,000 total costs per year (including 8% F&A costs) for the number of years remaining in the project period of the parent award.

The NIDCR will provide supplements to grantee institutions to cover the training-related costs for oral health professionals or researchers per year, up to a total of $200,000 per year.

The deadline for receipt of letters of intent is 17 November 2004, with 16 December 2004 the deadline for receipt of applications. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Complete information on this RFA is located at http://grants1.nih.gov/grants/guide/rfa-files/RFA-TW-04-001.html.

Contact: Barbara Sina, Division of International Training and Research, FIC, 31 Center Dr, Rm B2C39, MSC 2220, Bethesda, MD 20892-2220 USA, 301-402-9467, fax: 301-402-0779, e-mail: sinab@mail.nih.gov. Reference: RFA No. RFA-TW-04-001